Structure–Activity Relationship Studies on Derivatives of Eudesmanolides from *Inula helenium* as Toxicants against *Aedes aegypti* Larvae and Adults

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An *Aedes aegypti* larval toxicity bioassay was performed on compounds representing many classes of natural compounds including polyacetylenes, phytosterols, flavonoids, sesquiterpenoids, and triterpenoids. Among these compounds, two eudesmanolides, alantolactone, and isoalantolactone showed larvicidal activities against *Ae. aegypti* and, therefore, were chosen for further structure–activity relationship study. In this study, structural modifications were performed on both alantolactone and isoalantolactone in an effort to understand the functional groups necessary for maintaining and/or increasing its activity, and to possibly lead to more effective insect-control agents. All parent compounds and synthetic modification reaction products were evaluated for their toxic activities against *Ae. aegypti* larvae and adults. Structure modifications included epoxidations, reductions, catalytic hydrogenations, and *Michael* additions to the α,β-unsaturated lactones. None of the synthetic isomers synthesized and screened against *Ae. aegypti* larvae were more active than isoalantolactone itself which had an LC_{50} value of 10.0 μg/ml. This was not the case for analogs of alantolactone for which many of the analogs had larvicidal activities ranging from 12.4 to 69.9 μg/ml. In general, activity trends observed from *Ae. aegypti* larval screening were not consistent with observations from adulticidal screening. The propylamine *Michael* addition analog of alantolactone was the most active adulticide synthesized with an LC_{50} value of 1.07 μg/mosquito. In addition, the crystal structures of both alantolactone and isoalantolactone were determined using CuK_α radiation, which allowed their absolute configurations to be determined based on resonant scattering of the light atoms.

1. Introduction. – The yellow fever mosquito, *Aedes aegypti* (L.; Diptera: Culicidae), transmits viral pathogens of humans, including yellow fever [1–4] and dengue [5–8], both of which can cause severe human morbidity and mortality. Although there is a safe and effective vaccine for the yellow fever virus, epidemic transmission still occurs in Africa with sporadic cases in South America [9–13]. Dengue is the most important arboviral disease in the world, causing an undifferentiated fever, dengue fever, dengue hemorrhagic fever, or dengue shock syndrome [14]. Annually, dengue epidemics cause several million cases and thousands of deaths worldwide [15].

Mosquito control in many countries relies primarily on insecticides. Following the introduction of synthetic organic insecticides in the 1940s and 1950s, *Ae. aegypti* was eradicated from many areas of the world. The *Pan American Health Organization* initiated a campaign to use DDT to eradicate *Ae. aegypti* in the Western Hemisphere in

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the late 1940s [16][17]. By 1972, *Ae. aegypti* had been eradicated from 73% of the land area and 19 countries [18]. However, insecticide resistance developed [19], and the campaign ended in 1972 before the eradication goal was achieved. Insecticide resistance has resulted in significant loss of efficacy to commonly used insecticides [20–24]. Therefore, there is an urgent need for the development of alternative insecticides to control these important disease vectors.

One potential source of new pesticides is natural plant chemicals. Not only might certain natural plant products be a source of new pesticides, but also botanical derivatives may be more environmentally friendly than synthetic chemicals [25]. This project began by randomly screening previously isolated and identified natural products from our personal repositories. The compounds chosen were representative of particular classes of natural products we had previously reported [26–29]. This screening approach led to a previously investigated set of eudesmanolides which were the subject of a structure–activity investigation. In particular, the two eudesmanolides, alantolactone and isoalantolactone, were the subject of this investigation. The larvicidal and adulticidal activities of all synthetic isomers, and analogs of alantolactone and isoalantolactone against *Ae. aegypti* and the structure–activity relationships are reported here.

2. Results and Discussion. – *Initial Compound Screening.* In an effort to identify novel classes of plant natural products with activity against *Ae. aegypti*, a high-throughput larval screening method [30] was performed on compounds representing many classes of natural compounds (*Table 1*). Representatives of polyacetylenes, phytosterols, flavonoids, sesquiterpenoids, and triterpenoids, among others, were

Table 1. *Larvicidal Activities of Various Natural Compounds against First Instar Larvae of* Ae. aegypti

	Mortality [%][a])				
	125 ppm	62.5 ppm	31.25 ppm	15.625 ppm	8 ppm
(*Z*,*Z*)-Matricaria ester	100	100	75	0	0
(*E*)-Cinnamic acid	0	0	0	0	0
Locustol	100	75	0	0	0
Cumostrol	2	0	0	0	0
Parthenin	0	0	0	0	0
Dihydroparthenolide	0	0	0	0	0
Betulin	0	0	0	0	0
Quercetin	75	75	60	0	0
Parthenolide	0	0	0	0	0
Rutin	0	0	0	0	0
Enhydrin	0	0	0	0	0
Ferulic acid	0	0	0	0	0
(24*R*)-24,25-Epoxycycloartan-3-one	0	0	0	0	0
Alantolactone (**1a**)	100	62.5	5.8	0	0
Isoalantolactone (**2a**)	100	100	100	100	20
Ergosterol endoperoxide	0	0	0	0	0

[a]) Evaluations also performed at 4, 2, and 1 ppm with 0% mortality for all treatments.

evaluated from 125 down to 2 ppm in a dose-dependent manner. Percent mortality was determined for evaluated compounds. Of the 16 compounds evaluated, five of these compounds gave 75% mortality or higher at 125 ppm. (*Z*,*Z*)-Matricaria ester was active down to 31.25 ppm, locustol down to 62.5 ppm, quercetin down to 31.25 ppm, alantolactone (**1a**) down to 31.25 ppm, and isoalantolactone (**2a**; *Fig. 1*) down to 8 ppm. On the basis of the above pre-screen, a structure–activity relationship study was initiated on the sesquiterpene eudesmanolides alantolactone (**1a**) and isoalantolactone (**2a**) in an effort to both understand the activity of these compounds and quite possibly produce more active isomers and analogs.

X-Ray Crystal-Structure Determinations. Prior to initiating the structure–activity

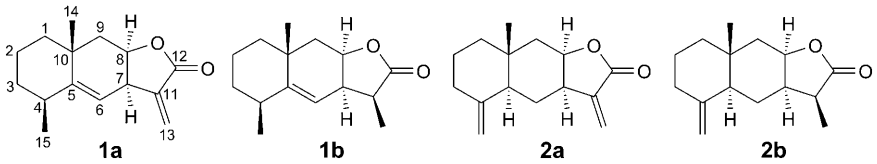


Fig. 1. *Compounds isolated from* Inula helenium. Arbitrary numbering.

relationship study, gram quantities of both alantolactone (**1a**) and isoalantolactone (**2a**) were needed, and purification was performed essentially as described in [27]. As previously observed, both compounds readily crystallized thus assisting in the purification of sufficient quantities for this synthetic study. X-Ray crystal-structure determinations were carried out for both compounds **1a** (*Fig. 2*) and **2a** (*Fig. 3*). The relatively new *Hooft* analysis of *Bijvoet* pairs [31] enabled the conclusive determination

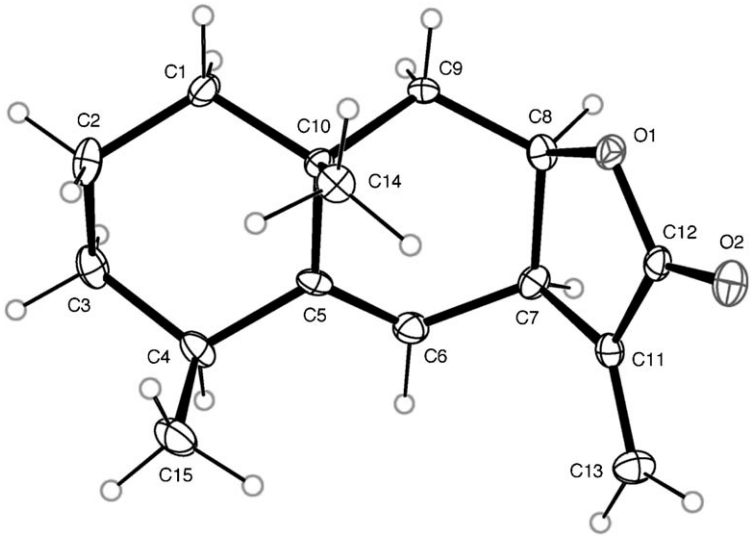


Fig. 2. *ORTEP Drawing of alantolactone* (**1a**)

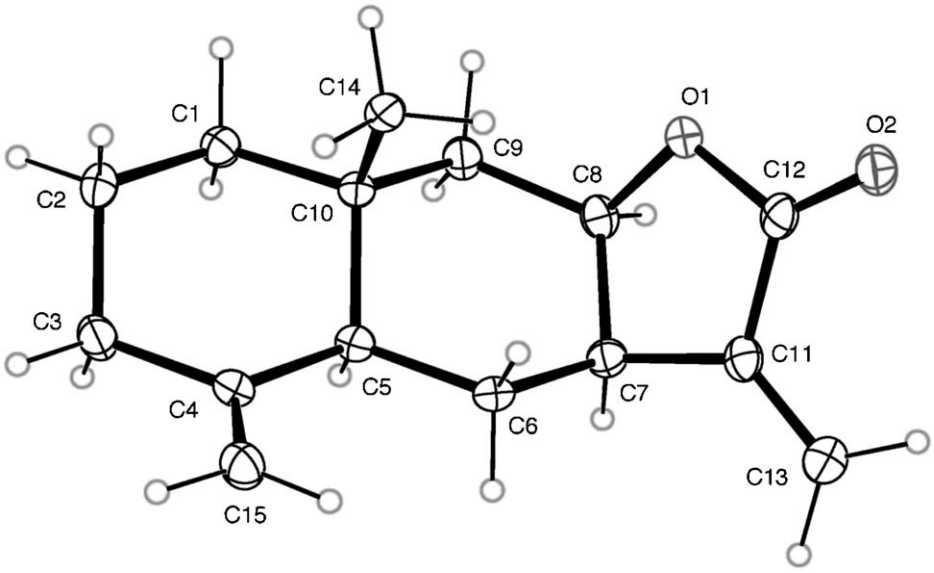


Fig. 3. *ORTEP Drawing of isoalantolactone* (**2a**)

of their absolute configurations by resonant scattering of the light atoms in CuK_α radiation. Details are given in the *Exper. Part*. Despite the fact that both **1a** and **2a** have been reported in the literature for at least half a century, a report on the X-ray crystal-structure determination was not found and is reported here for the first time.

Peracid Epoxidations. Compounds 11,13-dihydroalantolactone (**1b**) and 11,13-dihydroisoalantolactone (**2b**) were included in this study, as they were natural isomers which had been previously isolated by the authors [27]. Both compounds demonstrated LC_{50} values of >125 μg/ml against larvae of *Ae. aegypti* indicating the importance of the α,β-unsaturated lactone moiety (*Table 2*). Initial synthetic modifications included the peracid epoxidation of compounds **1a**, **2a**, **1b**, and **2b** to their corresponding epoxides **1c**, **2c**, **1d**, and **2d**, respectively (*Fig. 4*). Details on the synthesis of **1c**, **2c**, and **1d** had been reported in [27]. Similar yields were obtained for the synthesis of **2d** as previously performed and was greater than 100% due to inefficient washing. The presence of remaining peracid and/or acid was visible in both ^{1}H- and ^{13}C-NMR spectra of the product. All four epoxy synthetic isomers were also inactive up to the top testing concentration of 125 μg/ml.

Reductions. Additional modifications were performed on **1b** and included a catalytic hydrogenation to produce the desired product **1e** in a 63% yield. $LiAlH_4$ Reduction was also performed on **1b** in an attempt to synthesize its corresponding lactone hydrolysis product. Unfortunately, the diol **1f** was instead produced in low yield (48.7%). Derivatives **1e** and **1f** were evaluated in the *Ae. aegypti* larval screens, and both were inactive up to the top testing concentration of 125 μg/ml.

Michael *Additions.* The remaining set of modifications during this first batch of modifications (*Table 2*) to **1a** and **2a** targeted the α,β-unsaturated lactone moiety (*Fig. 5*). Specifically, *Michael* addition reactions using the nucleophilic amines

Table 2. *Larval* LC_{50} *Values* [μg/ml] *of Various Analogs of Isoalantolactone and Alantolactone against* Ae. aegypti

Batch[a])	Compound	LC_{50} (95% CI)	Slope (SE)	χ^2	df
1st	**1a**	36.2 (32.3–40.5)	9.04 (1.28)	13.58	10
	2a	10.0 (8.63–11.8)	6.75 (0.92)	19.12	10
	2b	>125			
	1b	>125			
	1c	>125			
	2c	>125			
	2d	>125			
	1d	>125			
	1e	>125			
	1f	>125			
	4a	14.4 (12.2–17.2)	9.59 (1.54)	25.93	10
	3a	>125			
	4b	55.1 (37.1–92.5)	2.50 (0.35)	5.82	4
	3b	12.4 (9.75–16.1)	6.73 (0.86)	40.09	10
2nd	**4c**	19.3 (15.3–22.5)	3.82 (0.63)	1.66	4
	3c	21.4 (16.2–27.4)	5.62 (0.72)	30.97	9
	4d	41.9 (26.5–57.3)	2.79 (0.44)	6.46	4
	3d	17.3 (13.2–21.3)	5.87 (0.83)	28.82	10
	4e	64.8 (44.4–95.8)	5.05 (0.62)	56.41	10
	3e	24.1 (17.4–37.9)	5.36 (0.82)	24.99	7
	4f	>125			
	3f	>125			
	4g	16.6 (14.5–18.9)	7.43 (0.95)	21.42	13
	3g	42.3 (34.4–51.7)	6.51 (0.85)	7.17	4
3rd	**3h**	29.9 (21.8–42.3)	3.36 (0.47)	7.65	4
	4h	108 (94.1–136)	7.22 (1.33)	16.71	10
	4i	24.3 (20.4–29.2)	6.84 (0.87)	23.91	10
	3i	31.5 (22.7–44.4)	4.81 (0.58)	46.17	10
	4j	55.0 (49.4–61.1)	9.79 (1.57)	12.93	10
	3j	35.6 (32.3–39.4)	6.27 (0.82)	9.16	10
	4k	19.7 (17.9–21.9)	7.44 (1.06)	6.50	9
	3k	20.6 (18.0–23.7)	7.59 (1.03)	16.56	10
	4l	30.5 (27.3–33.8)	8.47 (1.36)	10.83	10
	3l	31.0 (22.8–41.8)	5.07 (.061)	42.43	10
	4m	35.6 (30.8–41.3)	5.95 (0.76)	14.91	10
	3m	69.9 (57.7–88.8)	3.09 (0.45)	11.89	10

[a]) Data is organized in series by batches tested and synthesized.

piperidine and diethylamine (Et_2NH) were performed on both compounds **1a** and **2a**. Additions of Et_2NH to both **1a** and **2a** produced the desired products **3a** and **4a** in yields of 53.3 and 61.6%, respectively. Additions of piperidine to **1a** and **2a** provided the desired products **3b** and **4b** in yields of 65.7 and 78.4%, respectively. *Ae. aegypti* larvicidal activity for the diethylamino analogs were 14.4 and >125 μg/ml for **4a** and **3a**, respectively. Compound **4a** is only slightly less active than its parent compound **2a**. Piperidine analogs **4b** and **3b** were both active against *Ae. aegypti* larvae with LC_{50}

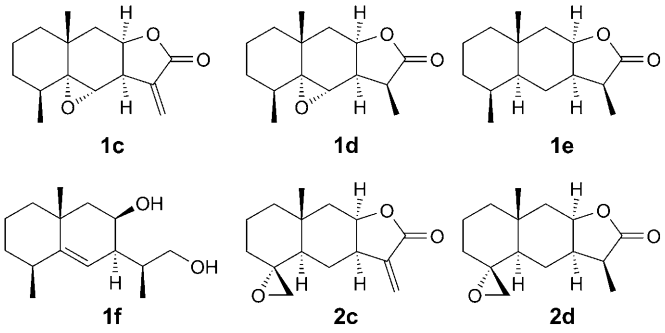
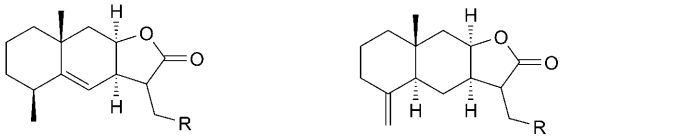


Fig. 4. *Synthetic epoxidation and reduction reaction products*



3a R = diethylamino
3b R = piperidin-1-yl
3c R = nonylamino
3d R = pyrrolidin-1-yl
3e R = benzylamino
3f R = (3-chlorobenzyl)(methyl)amino
3g R = (pyridin-4-yl)sulfanyl
3h R = propylamino
3i R = hexylamino
3j R = butylamino
3k R = decylamino
3l R = undecylamino
3m R = dodecylamino

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4h R = propylamino
4i R = hexylamino
4j R = butylamino
4k R = decylamino
4l R = undecylamino
4m R = dodecylamino

Fig. 5. Michael *addition reaction products of alantolactone* (**1a**) *and isoalantolactone* (**2a**)

values of 55.1 and 12.4 μg/ml, respectively. On the basis of the above screening for this first batch of analogs, *Michael* addition synthetic isomers and analogs will be the target of the remainder of this SAR study.

The second batch of analogs consists of a variety of nitrogen and sulfur nucleophiles reacted with both **1a** and **2a** to produce the desired *Michael* addition products. Nitrogen nucleophiles included the primary amine nonylamine, pyrrolidine, benzylamine, and 3-chloro-*N*-methylbenzyl amine, and the only sulfur nucleophile in the study was 4-sulfanylpyridine (*Fig. 5*). Nonylamine reaction products **3c** and **4c** were produced in yields of 70.3 and 77.9%, and larvicidal activities were 21.4 and 19.3 μg/ml, respectively (*Table 2*). Pyrrolidine analogs **3d** and **4d** were produced in yields of 71.2 and 70.0%, and larvicidal activities were 17.3 and 41.9 μg/ml, respectively. Benzylamine analogs **3e** and **4e** were produced in yields of 56.7 and 50.8%, and larvicidal activities were 24.1 and 64.8 μg/ml, respectively. These yields were the lowest of any of the *Michael* addition products. The reaction of the chlorinated nucleophile, 3-chloro-*N*-methylbenzyl amine,

afforded products **3f** and **4f** in yields of 67.3 and 94.2%, and larvicidal screening revealed that both compounds were inactive up to 125 μg/ml. The two sulfur-nucleophile reaction products **3g** and **4g** were produced in yields of 82.1 and 66.8%, and larvicidal activities were 42.3 and 16.6 μg/ml, respectively.

The third batch of analogs synthesized contained linear saturated alkylamino groups from propyl up to dodecyl (*Fig. 5*). Yields for these reactions ranged from a low of 42% for the *Michael* addition reaction of undecylamine with **1a** to a high of nearly 100% for the reaction of propylamine with **2a**. Larvicidal screening against *Ae. aegypti* for these linear alkylamino derivatives revealed that all were active within the range tested (*Table 2*). The LC_{50} values ranged from a low of 19.3 μg/ml for the nonylamine isoalantolactone adduct, **4c**, to a high of 108 μg/ml for the propylamine isoalantolactone adduct, **4h**.

Ae. aegypti *Larvicidal Screening.* An empirical analysis of the screening results described above for the reactions of linear amines with both **1a** and **2a** led us to create a plot of *Ae. aegypti* larvicidal LC_{50} values *vs.* the number of C-atoms in the linear amines (*Fig. 6*). Results of screening propylamino analogs were intentionally omitted due to its distortion of the trend when plotted; however, all remaining linear alkylamino analogs from butylamine up to dodecylamine were included. Clearly, there appears to be a relationship between the *Ae. aegypti* larvicidal activity and the number of C-atoms in the linear amine and/or chain length of the linear amine. For the plotting of activity *vs.* the number of C-atoms for alantolactone isomers, and subsequent addition of a second-order polynomial trendline, it becomes clear that seven to eight C-atoms in the amine is the optimum number needed to maximize activity. Similarly for isoalantolactone isomers, the trendline and plotting indicates that nine C-atoms would be the optimal number of C-atoms for the highest activity.

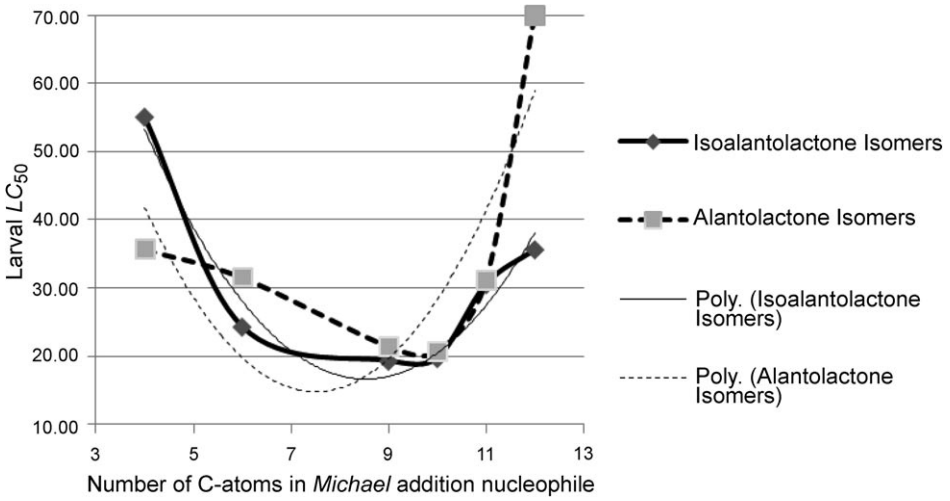

Fig. 6. *C_4 to C_{12} aliphatic* Michael-*addition substituted reaction products* vs. *larval* LC_{50} *activity.* Corresponding second-order polynomial regression lines are overlaid.

Ae. aegypti *Adulticidal Activity.* Lastly, all compounds were evaluated for activity against adult *Ae. aegypti* mosquitoes (*Table 3*). The LC_{50} values for **1a** and **2a** were 5.16 and 2.28 μg/mosquito, respectively, which follows the trend observed for *Ae. aegypti* larvicidal screening that **2a** is more active than **1a**. The epoxy analogs of **1a** and **2a**, namely **1c** and **2c**, respectively, were both active against adult mosquitoes. Compound **1c** was more active than its parent compound alantolactone (**1a**) with a value of 1.39 μg/mosquito. The diethylamino analogs of **1a** and **2a**, namely **3a** and **4a**, respectively, were also both active against adult mosquitoes. Again, the analog **3a** was more active than its parent compound **1a** with a value of 1.42 μg/mosquito. The propylamine analog of alantolactone (**1a**), compound **3h**, was the most active adulticide synthesized with an LC_{50} value of 1.07 μg/mosquito. The hexylamino analogs of both **1a** and **2a** were both highly active against adults with LC_{50} values of 1.34 and 1.76 μg/mosquito for **3i** and **4i**, respectively.

Table 3. *Adulticidal Activities of Isoalantolactone and Alantolactone Isomers against* Ae. aegypti

Compound[a])	LC_{50} (95% CI) [μg/mosquito]	Slope (SE)	χ^2[b])
1a	5.16 (4.66–5.67)	6.76 (0.95)	9.32[c])
2a	2.28 (1.99–2.56)	5.21 (0.76)	12.37[c])
1c	1.39 (1.24–1.56)	5.52 (0.86)	2.15
2c	2.05 (1.82–2.45)	5.87 (1.13)	0.95
4a	2.29 (1.99–2.99)	5.33 (1.14)	1.66
3a	1.42 (1.15–1.79)	6.98 (1.08)	4.25
3h	1.07 (0.95–1.18)	6.30 (0.97)	1.20
4i	1.76 (1.56–2.07)	4.90 (0.86)	0.42
3i	1.34 (1.21–1.49)	4.80 (0.74)	0.537

[a]) All isomers in this study were evaluated. All compounds not shown in this *Table* had LC_{50} values higher than 2.34 mg/mosquito. Only compound **1a** was evaluated at higher concentrations. [b]) df = 3. [c]) df = 13.

Overall, none of the synthetic isomers screened against *Ae. aegypti* larvae were more active than isoalantolactone (**2a**) itself. This was not the case for analogs of alantolactone (**1a**) for which many of the analogs had good larvicidal activity. In general, activity trends observed from *Ae. aegypti* larval screening were not consistent with observations from adulticidal screening. For example, the most active compound in the adulticidal screen was the propylamino analog of alantolactone (**1a**), compound **3h**, whereas the most active compound in the larvicidal screen was isoalantolactone (**2a**). This could be due to the entry-route differences between the two bioassay systems, *i.e.*, in adult bioassays, compounds enter only through the cuticle, while, in larval assays, compounds can either be absorbed through the cuticle or enter *via* the midgut.

Experimental Part

General. Column chromatography (CC): *Biotage*, *Inc. Horizon*™ pump (Charlottesville, Virginia) equipped with a *Horizon*™ flash collector and fixed wavelength (254 nm) detector. HPLC Method

development work was performed using an *Agilent 1100* system equipped with a quaternary pump, autosampler, diode-array detector, and vacuum degasser. Semi-prep. HPLC: *Waters Delta-Prep* system (Milford, MA) equipped with a diode-array detector and a binary pump. ^{1}H- and ^{13}C-NMR spectra: *Varian ANOVA 400* MHz or *Varian Unity INOVA 600* MHz spectrometer (Palo Alto, CA); in $CDCl_3$ or C_6D_6; all ^{13}C multiplicities were deduced from 90° and 135° DEPT experiments. HR-MS: *Agilent 1100* HPLC coupled to a *JEOL AccuTOF* (*JMS-T100LC*) (Peabody, MA).

High-Resolution LC/MS Analysis. All isolated and synthetic compounds were prepared in MeOH and injected directly into a 0.3-ml/min stream of either MeOH or 80% MeOH/20% deionized (DI) H_2O. Twenty µl of sample (*ca.* 0.1 mg/ml) was injected manually at 0.5 min, while mass drift compensation standards (L-tryptophan (neg. ion), PEG (pos. ion)) were injected at 1.5 min over the course of a 2-min run isocratic.

GC/MS Analysis. Analogs and reaction intermediates were analyzed by GC/MS on a *Varian CP-3800* GC coupled to a *Varian Saturn 2000* MS/MS. GC was equipped with a *DB-5* column (30 m × 0.25 mm fused silica cap. column, film thickness of 0.25 µm) operated using the following conditions: injector temp., 240°; column temp., 60–240° at 3°/min then held at 240° for 5 min; carrier gas, He; injection volume, 1 µl (splitless). MS Mass range from 40 to 650 *m*/*z*, filament delay of 3 min, target TIC of 20,000, a prescan ionization time of 100 µs, an ion-trap temp. of 150°, manifold temp. of 60°, and a transfer line temp. of 170°.

Alantolactone (=*(3a*R,*5*S,*8a*R,*9a*R*)-3a,5,6,7,8,8a,9,9a-Octahydro-5,8a-dimethyl-3-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one*; **1a**), *Isoalantolactone* (=*(3a*R,*4a*S,*8a*R,*9a*R*)-Decahydro-8a-methyl-3,5-dimethylidenenaphtho[2,3-*b*]furan-2(3*H*)-one*; **2a**), *11,13-Dihydroalantolactone* (=*(3*S,*3a*R,*5*S,*8a*R,*9a*R*)-3a,5,6,7,8,8a,9,9a-Octahydro-3,5,8a-trimethylnaphtho[2,3-*b*]furan-2(3*H*)-one*; **1b**), *and 11,13-Dihydroalantolactone* (=*(3*S,*3a*R,*4a*S,*8a*R,*9a*R*)-Decahydro-3,8a-dimethyl-5-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one*; **2b**). Information on the collection, identification, and voucher deposition for *Inula helenium* have been reported in [16]. Details on the isolation and identification of compounds **1a**, **2a**, **1b**, and **2b** from *I. helenium* have been reported in [27].

X-Ray Crystallographic Data for Alantolactone (**1a**). The crystal structure was determined using X-ray data collected at 90 K, with CuK_α radiation ($\lambda = 1.54178$ Å) on a *Bruker Kappa Apex-II* diffractometer. Crystals are orthorhombic, space group $P2_12_12_1$ with $Z = 4$. All H-atoms were visible in difference maps, and were placed in calculated positions in the refinement, with a torsional parameter refined for each Me group, leading to $R = 0.049$, $R_w = 0.123$ for 215 refined parameters and 2272 independent reflections having $\theta_{max} = 68.8°$. The absolute configuration was determined, based on resonant scattering from light atoms only, to be that shown in *Fig. 2*, using *904 Bijvoet* pairs. The *Flack* [32] parameter has a value of $x = 0.1(3)$, and the *Hooft* [31] parameter has a value of $y = 0.11(9)$, corresponding to a probability of 1.000 that the reported absolute configuration is correct. The CIF has been deposited with the *Cambridge Crystallographic Data Centre*, CCDC-752255.

X-Ray Crystallographic Data for Isoalantolactone (**2a**). The crystal structure was determined, including absolute configuration, as for **1a**. Crystals are monoclinic, space group $P2_1$ with $Z = 2$, $R = 0.023$, $R_w = 0.062$ for 215 refined parameters and 2192 independent reflections having $\theta_{max} = 68.6°$. The absolute configuration determination was based on 956 *Bijvoet* pairs, *Flack* parameter $x = 0.01(16)$, *Hooft* parameter $y = 0.05(5)$, corresponding to a probability of 1.000 that the reported absolute configuration is correct. The CIF has been deposited with the *Cambridge Crystallographic Data Centre*, CCDC-752256.

meta-*Chloroperbenzoic Acid (*m-*CPBA) Oxidation of* **1a**, **2a**, *and* **1b**. Details on the *m*-CPBA oxidation of **1a**, **2a**, and **1b** to their corresponding epoxides **1c**, **2c**, and **1d**, resp., have been reported in [27].

m-*CPBA Oxidation of* **2b**. A soln. of 156.0 mg of **2b** in 20 ml of CH_2Cl_2 was added to 275.6 mg of *m*-CPBA in an ice-bath overnight. The mixture was washed two times with 20 ml of 10% aq. $NaHCO_3$ and twice with 20 ml of deionized H_2O. Products were separated by SiO_2 CC on a *Biotage 40 + M* column (40–63 µm, 60 Å, 25 × 150 mm) running at 40 ml/min using a hexanes/AcOEt step gradient beginning with 100 : 0 to 75 : 25 over 1152 ml and finishing with 75 : 25 to 50 : 50 over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one fraction with one distinct compound. Drying provided 241.2 mg of pure *(3*S,*3a*R,*4a*R,*5*R,*8a*R,*9a*R*)-3,8a-dimethyldecahydro-2*H*-spiro[naphtho[2,3-*b*]furan-5,2′-oxiran]-2-one* (**2d**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.41 (br. *s*, 1 H); 2.71–2.76 (*m*,

1 H); 2.66 (*d*, *J* = 4.0, 1 H); 2.53 (*d*, *J* = 4.0, 1 H); 2.25–2.31 (*m*, 1 H); 2.11 (*d*, *J* = 15.6, 1 H); 1.10 (*d*, *J* = 7.2, 3 H); 0.90 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 179.6 (*s*); 77.7 (*d*); 58.9 (*s*); 51.0 (*t*); 44.6 (*d*); 42.2 (*t*); 41.8 (*d*); 41.5 (*t*); 40.4 (*d*); 35.4 (*t*); 34.9 (*s*); 20.5 (*t*); 18.8 (*q*); 17.0 (*t*); 9.4 (*q*). EI-MS (70 eV): 250 (3, M^+), 236 (15), 235 (100), 147 (11), 91 (9). HR-ESI-MS: 273.1423 ($[M+Na]^+$, $C_{15}H_{22}NaO_3^+$; calc. 273.1467), 523.3046 ($[2M+Na]^+$, $C_{30}H_{44}NaO_6^+$; calc. 523.3036).

Catalytic Hydrogenation of **1b**. Compound **1b** (51.9 mg) was dissolved in 10 ml of MeOH in a 250-ml round-bottom flask. Two spatula tips full of 5% Pd/C was added to the mixture and charged with H_2 with stirring for 3 d. The mixture was filtered through a bed of *Celite 545* and washed with CH_2Cl_2. The products were purified using normal-phase chromatography *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min hexanes/AcOEt step gradient beginning with 100 : 0 to 75 : 25 over 1152 ml and finishing with 75 : 25 to 50 : 50 over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into two distinct compounds. Drying provided 33.6 mg of pure *(3*S*,3a*R*,4a*S*,5*S*,8a*R*,9a*R*)-3,5,8a-trimethyldecahydronaphtho[2,3-*b*]furan-2(3*H*)-one* (**1e**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.36 (br. *s*, 1 H); 2.65–2.72 (*m*, 1 H); 2.30–2.33 (*m*, 1 H); 1.87 (*d*, *J* = 15.0, 1 H); 1.12 (*d*, *J* = 6.6, 3 H); 0.89 (*s*, 3 H); 0.80 (*d*, *J* = 7.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 179.7 (*s*); 78.3 (*d*); 45.3 (*t*); 44.1 (*d*); 42.2 (*t*); 41.6 (*d*); 41.2 (*d*); 33.6 (*t*); 33.2 (*d*); 33.0 (*s*); 24.5 (*t*); 21.1 (*q*); 16.8 (*t*); 14.7 (*q*); 9.3 (*q*). EI-MS (70 eV): 237 (64, M^+), 219 (25), 192 (19), 177 (100), 163 (86), 147 (38), 135 (26), 109 (50). HR-ESI-MS: 237.1899 ($[M+H]^+$, $C_{15}H_{25}O_2^+$; calc. 237.1854, 259.1688 ($[M+Na]^+$, $C_{15}H_{24}NaO_2^+$; calc. 259.1674, 495.3470 ($[2M+Na]^+$, $C_{30}H_{48}NaO_4$; calc. 495.3450).

$LiAlH_4$ Reduction of **1b**. Compound **1b** (90.2 mg) was dissolved in 5 ml of anh. THF and transferred to a dry 100-ml round-bottom flask with a magnetic stirrer. To this soln., 215.5 mg of $LiAlH_4$ were slowly added in an ice-bath, followed by 8 ml of THF. The mixture was refluxed overnight with the addition of 205.6 mg of $LiAlH_4$ dissolved in 2 ml of THF. The mixture was stirred under reflux overnight. The reaction was complete in 2 d at which time *ca.* 25 ml of deionized H_2O was added dropwise to quench the reaction. This mixture was extracted three times with 25 ml of Et_2O. After removal of organics *in vacuo*, the residue (79.6 mg) was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 100 : 0 to 50 : 50 over 1728 ml, followed by 50 : 50 to 0 : 100 over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into three distinct fractions (*A*–*C*). *Fr. B* provided 45.9 mg of pure *(2*R*,3*R*,5*S*,8a*R*)-1,2,3,5,6,7,8,8a-octahydro-3-[(2*S*)-1-hydroxypropan-2-yl]-5,8a-dimethylnaphthalen-2-ol* (**1f**). ^{1}H-NMR (600 MHz, $CDCl_3$): 5.20 (br. *s*, 1 H); 4.06 (br. *s*, 1 H); 3.55–3.65 (*m*, 1 H); 3.47 (*dd*, *J* = 3.6, 9.0, 1 H); 2.41–2.48 (*m*, 1 H); 2.25–2.27 (*m*, 1 H); 1.29 (*s*, 3 H); 1.12 (*d*, *J* = 7.2, 3 H); 0.99 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 148.4 (*s*); 118.0 (*d*); 68.3 (*d*); 65.2 (*t*); 48.2 (*t*); 45.1 (*d*); 43.1 (*t*); 39.4 (*d*); 37.2 (*d*); 34.5 (*s*); 33.8 (*t*); 28.6 (*q*); 22.5 (*q*); 17.4 (*t*); 17.3 (*q*). EI-MS (70 eV): 239 (100, M^+), 221 (78), 203 (49), 189 (53), 161 (31), 139 (21), 105 (27). HR-ESI-MS: 477.3973 ($[2M+H]^+$, $C_{30}H_{53}O_4^+$; calc. 477.3943).

Michael *Addition of Et_2NH and* **2a**. A soln. of 51.5 mg of **2a** in 4 ml of 100% anh. EtOH was added to 100 μl of Et_2NH, and the soln. was stirred for 1 h at r.t. 400 μl of Et_2NH was added, and the mixture was refluxed overnight. The reaction was quenched with 3 ml of deionized H_2O, and the mixture was extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/Et_2O step gradient beginning with 100 : 0 to 0 : 100 over 1728 ml, followed by 100% Et_2O over 1728 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 41.7 mg of pure *(3a*R*,4a*S*,8a*R*,9a*R*)-3-[(diethylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one* (**4a**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.70 (*s*, 1 H); 4.43 (br. *s*, 1 H); 4.39 (*s*, 1 H); 2.93–2.96 (*m*, 1 H); 1.02 (*t*, *J* = 7.2, 6 H), 0.736 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.9 (*s*); 149.4 (*s*); 106.4 (*t*); 78.4 (*d*); 47.9 (*t*); 47.1 (*t*); 46.5 (*d*); 45.6 (*d*); 42.3 (*t*); 41.6 (*t*); 39.2 (*d*); 36.8 (*t*); 34.8 (*s*); 22.7 (*t*); 21.4 (*t*); 17.9 (*q*); 11.2 (*q*). EI-MS (70 eV): 306 (12, M^+), 290 (19), 276 (11), 86 (100), 72 (17), 58 (8). HR-ESI-MS: 306.2420 ($[M+H]^+$, $C_{19}H_{32}NO_2^+$, calc. 306.2433).

Michael *Addition of Et_2NH and* **1a**. A soln. of 53.4 mg of **1a** in 4 ml of 100% abs. EtOH was added to 600 μl of Et_2NH, and the mixture was stirred at r.t. over 3 d. 400 μl of Et_2NH was added, and the mixture was stirred for 4 h. The reaction was quenched with 3 ml of deionized H_2O, and the mixture was extracted

three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 36.1 mg of pure *(3a*R,*5*S,*8a*R,*9a*R*)-3-[(diethylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3a**). ^{1}H-NMR (600 MHz, $CDCl_3$): 5.37 (*s*, 1 H); 4.66–4.69 (*m*, 1 H); 3.05–3.08 (*m*, 1 H); 2.95–2.99 (*m*, 1 H); 1.18 (*s*, 3 H); 1.08 (*d*, *J* = 7.2, 3 H); 0.98 (*t*, *J* = 7.2, 7.2, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.9 (*s*); 150.7 (*s*); 116.1 (*d*); 77.5 (*d*); 49.3 (*t*); 46.8 (*t*); 44.1 (*d*); 43.1 (*t*); 42.5 (*t*); 38.8 (*d*); 38.1 (*d*); 33.2 (*s*); 33.1 (*t*); 28.8 (*q*); 23.2 (*q*); 17.1 (*d*); 11.5 (*q*). EI-MS (70 eV): 306 (7, M^+), 290 (13), 276 (4), 86 (100), 72 (6), 58 (8). HR-ESI-MS: 306.2428 ($[M+H]^+$, $C_{19}H_{32}NO_2^+$; calc. 306.2433.

Michael *Addition of Piperidine and* **2a**. A soln. of 51.2 mg of **2a** in 4 ml of 100% abs. EtOH was added to 200 μl of piperidine, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O, and the mixture was extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 54.9 mg of pure *(3a*R,*4a*S,*8a*R,*9a*R*)-decahydro-8a-methyl-5-methylidene-3-(piperidin-1-ylmethyl)naphtho[2,3-*b*]furan-2(3*H*)-one* (**4b**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.71 (*s*, 1 H); 4.39–4.42 (*m*, 1 H); 4.41 (*s*, 1 H); 2.87–2.92 (*m*, 1 H); 2.65 (*dd*, *J* = 3.6, 13.2, 1 H), 2.55 (*t*, *J* = 10.8, 1 H); 0.73 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.1 (*s*); 149.5 (*s*); 106.5 (*t*); 78.3 (*d*); 54.8 (*t*); 53.9 (*t*); 46.6 (*d*); 45.6 (*d*); 42.3 (*t*); 41.7 (*t*); 39.5 (*d*); 36.8 (*t*); 34.9 (*s*); 26.0 (*t*); 24.3 (*t*); 22.8 (*t*); 21.1 (*t*); 17.9 (*q*). EI-MS (70 eV): 318 (32, M^+), 98 (100). HR-ESI-MS: 318.2452 ($[M+H]^+$, $C_{20}H_{32}NO_2^+$; calc. 318.2433).

Michael *Addition of Piperidine and* **1a**. A soln. of 51.4 mg of **1a** in 4 ml of 100% abs. EtOH was added to 600 μl of piperidine, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 46.2 mg of pure *(3a*R,*5*S,*8a*R,*9a*R*)-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethyl-3-(piperidin-1-ylmethyl)naphtho[2,3-*b*]furan-2(3*H*)-one* (**3b**). ^{1}H-NMR (600 MHz, $CDCl_3$): 5.28 (*s*, 1 H); 4.65 (br. *s*, 1 H); 3.05–3.08 (*m*, 1 H); 2.98–3.01 (*m*, 1 H); 1.16 (*s*, 3 H); 1.06 (*d*, *J* = 7.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.9 (*s*); 150.7 (*s*); 116.0 (*d*); 77.4 (*d*); 55.0 (*t*); 43.8 (*d*); 43.0 (*t*); 42.4 (*t*); 38.7 (*d*); 38.2 (*d*); 33.2 (*t*); 33.0 (*s*); 28.7 (*q*); 26.1 (*t*); 24.4 (*t*); 23.1 (*q*); 17.1 (*t*). EI-MS (70 eV): 318 (27, M^+), 98 (100). HR-ESI-MS: 318.2439 ($[M+H]^+$, $C_{20}H_{32}NO_2^+$; calc. 318.2433.

Michael *Addition of Pyrrolidine and* **2a**. A soln. of 52.3 mg of **2a** in 4 ml of 100% abs. EtOH was added to 600 μl of pyrrolidine, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 μm, 60 Å, 40 × 150 mm) running at 40 ml/min using an isocratic method of 100% acetone over 1152 ml. 24-ml fractions were collected and recombined based on TLC similarities into two distinct fractions (*A* and *B*). *Fr. A* provided 47.8 mg of pure *(3a*R,*4a*S,*8a*R,*9a*R*)-decahydro-8a-methyl-5-methylidene-3-(pyrrolidin-1-ylmethyl)naphtho[2,3-*b*]furan-2(3*H*)-one* (**4d**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.72 (br. *s*, 1 H); 4.43 (*s*, 1 H); 4.40–4.45 (*m*, 1 H); 2.85–2.90 (*m*, 1 H); 2.81 (*t*, *J* = 12.6, 1 H); 2.72 (*dd*, *J* = 4.2, 12.6, 1 H); 0.75 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.7 (*s*); 149.4 (*s*); 106.4 (*t*); 78.3 (*d*); 54.4 (*t*); 50.9 (*t*); 47.1 (*d*); 46.6 (*d*); 42.3 (*t*); 41.6 (*t*); 39.3 (*d*); 36.8 (*t*); 34.9 (*s*); 23.6 (*t*); 22.8 (*t*); 21.1 (*t*); 17.9 (*q*). EI-MS (70 eV): 304 (15, M^+), 84 (100), 70 (5), 42 (6). HR-ESI-MS: 629.4299 ($[2M+Na]^+$, $C_{38}H_{58}N_2NaO_4^+$; calc. 629.4294).

Michael *Addition of Pyrrolidine and* **1a**. A soln. of 54.2 mg of **1a** in 4 ml of 100% abs. EtOH was added to 600 µl of pyrrolidine, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using an isocratic method of 100% acetone over 1152 ml. 24-ml fractions were collected and recombined based on TLC similarities into two distinct fractions (*A* and *B*). *Fr. B* provided 50.4 mg of pure *(3a*R,*5*S,*8a*R,*9a*R*)-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethyl-3-(pyrrolidin-1-ylmethyl)naphtho[2,3-*b*]furan-2(3*H*)-one* (**3d**). ^{1}H-NMR (600 MHz, $CDCl_3$): 5.30 (*d*, *J* = 3.0, 1 H); 4.66–4.70 (*m*, 1 H); 3.11–3.15 (*m*, 1 H); 2.95–3.00 (*m*, 1 H); 2.84 (*t*, *J* = 12.6, 1 H); 2.65 (*dd*, *J* = 4.2, 12.6, 1 H); 1.19 (*s*, 3 H); 1.09 (*d*, *J* = 7.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.4 (*s*); 150.8 (*s*); 115.8 (*d*); 77.4 (*d*); 54.2 (*t*); 52.0 (*t*); 45.4 (*d*); 43.0 (*t*); 42.4 (*t*); 38.7 (*d*); 38.1 (*d*); 33.2 (*d*); 33.0 (*t*); 28.7 (*q*); 23.7 (*t*); 23.1 (*q*); 17.0 (*t*). EI-MS (70 eV): 304 (14, M^+), 288 (9), 84 (100), 42 (6). HR-ESI-MS: 629.4304 ($[2M+Na]^+$, $C_{38}H_{58}N_2NaO_4^+$, 629.4294).

Michael *Addition of $PhCH_2NH_2$ and* **2a**. A soln. of 49.4 mg of **2a** in 4 ml of 100% abs. EtOH was added to 600 µl of $PhCH_2NH_2$, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O, and the mixture was extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 36.7 mg of pure *(3a*R,*4a*S,*8a*R,*9a*R*)-3-[(benzylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one* (**4e**). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.30–7.34 (*m*, 4 H); 7.21–7.26 (*m*, 1 H); 4.74 (*s*, 1 H); 4.44–4.46 (*m*, 1 H); 4.36 (*s*, 1 H); 3.79 (*d*, *J* = 13.8, 1 H); 3.70 (*d*, *J* = 13.2, 1 H); 0.69 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.1 (*s*); 149.2 (*s*); 128.6 (*d*); 128.3 (*d*); 127.2 (*d*); 106.6 (*t*); 78.4 (*d*); 54.1 (*t*); 47.4 (*d*); 46.5 (*d*); 44.7 (*t*); 42.3 (*t*); 41.5 (*t*); 39.1 (*d*); 36.8 (*t*); 34.8 (*s*); 22.7 (*t*); 21.1 (*t*); 17.9 (*q*). EI-MS (70 eV): 340 (33, M^+), 120 (14), 106 (100), 91 (29). HR-ESI-MS: 340.2297 ($[M+H]^+$, $C_{22}H_{30}NO_2^+$; calc. 340.2276), 679.4456 ($[2M+H]^+$, $C_{44}H_{59}N_2O_4^+$; calc. 679.4474). 701.4275 ($[2M+Na]^+$, $C_{44}H_{59}N_2NaO_4^+$; calc. 701.4294).

Michael *Addition of $PhCH_2NH_2$ and* **1a**. A soln. of 52.5 mg of **1a** in 4 ml of 100% abs. EtOH was added to 600 µl of $PhCH_2NH_2$ and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O, and the mixture was extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo* the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 43.5 mg of pure *(3a*R,*5*S,*8a*R,*9a*R*)-3-[(benzylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3e**). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.29–7.36 (*m*, 4 H); 7.21–7.26 (*m*, 1 H); 5.04–5.06 (*m*, 1 H); 4.69–4.71 (*m*, 1 H); 3.86 (*d*, *J* = 13.2, 1 H); 3.75 (*d*, *J* = 13.2, 1 H); 1.18 (*s*, 3 H); 1.03 (*d*, 3 H, *J* = 7.8). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.9 (*s*); 150.9 (*s*); 128.5 (*d*); 128.3 (*d*); 127.1 (*d*); 115.2 (*d*); 77.5 (*d*); 54.1 (*t*); 45.9 (*d*); 45.8 (*t*); 42.8 (*t*); 42.9 (*t*); 38.4 (*d*); 37.7 (*d*); 33.0 (*q*); 32.9 (*s*); 28.7 (*t*); 23.0 (*t*); 16.9 (*q*). EI-MS (70 eV): 340 (22, M^+), 322 (16), 120 (26), 106 (100), 91 (29), 65 (13). HR-ESI-MS: 340.2302 ($[M+H]^+$, $C_{22}H_{30}NO_2^+$; calc. 340.2276), 679.4467 ($[2M+H]^+$, $C_{44}H_{59}N_2O_4^+$; calc. 679.4474), 701.4291 ($[2M+Na]^+$, $C_{44}H_{59}N_2NaO_4^+$; calc. 701.4294).

Michael *Addition of 1-(3-Chlorophenyl)*-N-*methylmethanamine and* **2a**. A soln. of 56.5 mg of **2a** in 4 ml of 100% abs. EtOH was added to 600 µl of 3-chloro-*N*-methylbenzylamine and stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 100 : 0 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 88.9 mg of pure *(3a*R,*4a*-

S,*8a*R,*9a*R*)-3-{[(3-chlorobenzyl)(methyl)amino]methyl}decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one* (**4f**). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.24 (br. *s*, 1 H); 7.11–7.19 (*m*, 3 H); 4.67 (*s*, 1 H); 4.39 (*s*, 1 H); 4.20 (*s*, 1 H); 3.57 (*d*, *J* = 13.2, 1 H); 3.27 (*d*, *J* = 12.6, 1 H); 2.18 (*s*, 3 H); 0.70 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.5 (*s*); 148.9 (*s*); 129.6 (*d*); 129.0 (*d*); 127.3 (*d*); 127.1 (*d*); 106.5 (*t*); 78.2 (*t*); 62.2 (*t*); 52.2 (*t*); 46.4 (*d*); 45.7 (*d*); 42.4 (*q*); 42.2 (*t*); 41.5 (*t*); 38.9 (*d*); 36.7 (*t*); 34.7 (*s*); 22.7 (*t*); 20.7 (*t*); 17.8 (*q*). EI-MS (70 eV): 388 (28, M^+), 262 (10), 168 (100), 154 (21), 125 (24). HR-ESI-MS: 388.2040 ($[M+H]^+$, $C_{23}H_{31}ClNO_2^+$; calc. 388.2043), 410.1867 ($[M+Na]^+$, $C_{23}H_{30}ClNNaO_2^+$; calc. 410.1862), 797.3837 ($[2M+Na]^+$, $C_{46}H_{60}Cl_2N_2NaO_4^+$; calc. 797.3827).

Michael *Addition of 1-(3-Chlorophenyl)*-N-*methylmethanamine and* **1a**. A soln. of 46.7 mg of **1a** in 4 ml of 100% abs. EtOH was added to 600 µl of 3-chloro-*N*-methylbenzylamine, and stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40* + *M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 100 : 0 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 52.5 mg of pure *(3a*R,*5*-S,*8a*R,*9a*R*)-3-{[(3-chlorobenzyl)(methyl)amino]methyl}-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3f**). ^{1}H-NMR (600 MHz, $CDCl_3$): 7.30 (br. *s*, 1 H); 7.15–7.22 (*m*, 3 H); 5.10 (*s*, 1 H); 4.68 (*s*, 1 H); 3.63 (*d*, *J* = 13.2, 1 H); 3.26 (*d*, *J* = 12.6, 1 H); 2.24 (*s*, 3 H); 1.14 (*s*, 3 H); 0.92 (*d*, *J* = 7.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 177.3 (*s*); 150.9 (*s*); 129.6 (*d*); 129.2 (*d*); 127.5 (*d*); 127.4 (*d*); 115.5 (*d*); 77.4 (*d*); 62.4 (*t*); 53.4 (*t*); 44.0 (*d*); 42.9 (*t*); 42.4 (*q*); 42.3 (*t*); 38.4 (*d*); 37.8 (*d*); 33.0 (*t*); 32.9 (*s*); 28.7 (*q*); 23.1 (*q*); 16.9 (*t*). EI-MS (70 eV): 388 (16, M^+), 262 (4), 170 (33), 168 (100), 154 (11), 125 (15). HR-ESI-MS: 388.2025 ($[M+H]^+$, $C_{23}H_{31}ClNO_2^+$; 388.2043), 410.1870 ($[M+Na]^+$, $C_{23}H_{30}ClNNaO_2^+$; calc. 410.1862), 797.3826 ($[2M+Na]^+$, $C_{46}H_{60}Cl_2N_2NaO_4^+$; calc. 797.3827).

Michael *Addition of 4-Sulfanylpyridine and* **2a**. A soln. of 55.2 mg of **2a** in 4 ml of 100% abs. EtOH was added to 600 µl of a 25.0 mg/ml soln. of 4-sulfanylpyridine, and the mixture was stirred at 0° overnight. 2.4 ml of 25.0 mg/ml soln. of 4-sulfanylpyridine was added, and the mixture was stirred for 3 d. With no disappearance of starting material (*i.e.*, **2a**), 105.3 mg of 4-sulfanylpyridine powder was added, and the mixture was stirred overnight under reflux. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40* + *M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 100 : 0 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24-ml fractions were collected and recombined based on TLC similarities into two distinct fractions (*A* and *B*). *Fr. B* provided 54.5 mg of pure *(3a*R,*4a*S,*8a*R,*9a*R*)-decahydro-8a-methyl-5-methylidene-3-[(pyridin-4-ylsulfanyl)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**4g**). ^{1}H-NMR (600 MHz, $CDCl_3$): 8.33 (*s*, 2 H); 7.06 (*s*, 2 H); 4.68 (*s*, 1 H); 4.40 (br. *s*, 1 H); 4.36 (*s*, 1 H); 3.49 (*d*, *J* = 9.0, 1 H); 0.70 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 176.2 (*s*); 149.4 (*d*); 148.9 (*s*); 147.6 (*s*); 120.8 (*d*); 106.6 (*t*); 78.2 (*d*); 46.2 (*d*); 46.1 (*d*); 42.0 (*t*); 41.3 (*t*); 38.5 (*d*); 36.6 (*t*); 34.7 (*s*); 25.7 (*t*); 22.6 (*t*); 20.5 (*t*); 17.7 (*q*). EI-MS (70 eV): 344 (100, M^+), 182 (34), 147 (18), 105 (26), 79 (13), 41 (9). HR-ESI-MS: 344.1654 ($[M+H]^+$, $C_{20}H_{26}NO_2S^+$; calc. 344.1684), 366.1498 ($[M+Na]^+$, $C_{20}H_{25}NNaO_2S^+$; calc. 366.1503), 687.3634 $[2M+H]^+$, $C_{40}H_{51}N_2O_4S_2^+$; calc. 687.3290), 709.3169 $[2M+Na]^+$, $C_{40}H_{50}N_2NaO_4S_2^+$; calc. 709.3109).

Michael *Addition of 4-Sulfanylpyridine and* **1a**. A soln. of 48.5 mg of **1a** in 4 ml of 100% abs. EtOH was added to 202.4 mg of 4-sulfanylpyridine, and the mixture was stirred at r.t. overnight. 50.0 mg of 4-sulfanylpyridine was added, and the mixture was stirred overnight under reflux. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40* + *M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using a hexane/AcOEt step gradient beginning with 50 : 50 to 0 : 100 over 1152 ml, followed by 100% AcOEt over 576 ml. 24 ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided 58.9 mg of pure *(3a*R,*5*S,*8a*R,*9a*R*)-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethyl-3-[(pyridin-4-ylsulfanyl)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**3g**). ^{1}H-NMR (600 MHz, $CDCl_3$): 8.35 (*s*, 2 H); 7.10 (*s*, 2 H); 5.15 (*s*, 1 H); 4.67–4.69 (*m*, 1 H); 3.50 (*dd*,

J = 3.6, 13.2, 1 H); 1.15 (*s*, 3 H); 1.04 (*d*, J = 7.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 175.8 (*s*); 152.7 (*s*); 149.1 (*s*); 149.0 (*d*); 120.9 (*d*); 113.6 (*d*); 77.4 (*d*); 44.7 (*d*); 42.6 (*t*); 42.2 (*t*); 38.5 (*d*); 37.2 (*d*); 33.1 (*t*); 32.7 (*s*); 28.6 (*q*); 27.0 (*t*); 23.0 (*q*); 16.7 (*t*). EI-MS (70 eV): 344 (100, M^+), 162 (39), 105 (26), 91 (19), 51 (10). HR-ESI-MS: 344.1667 ($[M+H]^+$, $C_{20}H_{26}NO_2S^+$; 344.1684), 366.1501 ($[M+Na]^+$, $C_{20}H_{25}NNaO_2S^+$; calc. 366.1503), 687.3324 ($[2M+H]^+$, $C_{40}H_{51}N_2O_4S_2$; calc. 687.3290), 709.3169 ($[2M+Na]^+$, $C_{40}H_{50}N_2NaO_4S_2^+$; calc. 709.3147).

Michael *Addition of* **1a** *or* **2a** *and Linear Amines to Form Amine Adducts.* A soln. of the appropriate eudesmanolide (40–50 mg) in 4 ml of 100% abs. EtOH was added to 600 µl of amine, and the mixture was stirred overnight at 0°. The reaction was quenched with 3 ml of deionized H_2O and extracted three times with 20 ml of AcOEt. Products were dried ($MgSO_4$) and decanted into a 250-ml round-bottom flask. After removal of organics *in vacuo*, the residue was separated by SiO_2 CC on a *Biotage 40+M* column (40–63 µm, 60 Å, 40 × 150 mm) running at 40 ml/min using an isocratic method of 100% acetone over 1152 ml. 24-ml fractions were collected and recombined based on TLC similarities into one distinct compound. Drying provided pure compounds: **3h** (44.6 mg), **4h** (64.3 mg), **4i** (49.5 mg), **3i** (58.2 mg), **4j** (42.3 mg), **3j** (49.4 mg), **4k** (64.3 mg), **3k** (65.2 mg), **4l** (72.0 mg), **3l** (38.9 mg), **4m** (71.7 mg), and **3m** (74.1 mg), **4c** (64.7 mg), and **3c** (58.0 mg).

*(3a*R*,4a*S*,8a*R*,9a*R*)-Decahydro-8a-methyl-5-methylidene-3-[(nonylamino)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**4c**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.69 (br. *s*, 1 H); 4.39–4.44 (*m*, 1 H); 43.9 (br. *s*, 1 H); 2.92–2.96 (*m*, 1 H); 2.82–2.86 (*m*, 1 H); 2.67–2.72 (*m*, 1 H); 0.80 (*t*, 3 H, J = 7.2); 0.73 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.2 (*s*); 149.3 (*s*); 106.5 (*t*); 51.0 (*t*); 78.3 (*d*); 50.2 (*t*); 47.5 (*d*); 46.5 (*d*); 45.4 (*t*); 42.3 (*t*); 41.5 (*t*); 39.2 (*d*); 36.8 (*t*); 34.8 (*t*); 31.9 (*t*); 30.0 (*t*); 29.6 (*t*); 29.3 (*t*); 27.3 (*t*); 22.76 (*t*); 22.73 (*t*); 21.1 (*t*); 17.8 (*q*); 14.1 (*q*). EI-MS (70 eV): 376 (27, M^+), 262 (100), 156 (6), 142 (14), 91 (6), 44 (26). HR-ESI-MS: 376.3239 ($[M+H]^+$, $C_{24}H_{42}NO_2^+$; calc. 376.3215).

*(3a*R*,5*S*,8a*R*,9a*R*)-3a,5,6,7,8,8a,9,9a-Octahydro-5,8a-dimethyl-3-[(nonylamino)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**3c**). ^{1}H-NMR (600 MHz, $CDCl_3$): 5.11 (*d*, J = 2.4, 1 H); 4.67–4.71 (*m*, 1 H); 3.05–3.10 (*m*, 1 H); 1.18 (*s*, 3 H); 1.07 (*d*, J = 7.2, 3 H); 0.82 (*t*, J = 7.2, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.1 (*s*); 150.9 (*s*); 115.2 (*d*); 77.4 (*d*); 50.2 (*t*); 46.7 (*t*); 45.8 (*d*); 42.8 (*t*); 42.3 (*t*); 38.6 (*d*); 37.8 (*d*); 33.1 (*t*); 32.9 (*t*); 31.9 (*t*); 30.0 (*t*); 29.6 (*t*); 29.3 (*q*); 28.7 (*t*); 27.4 (*t*); 23.0 (*q*); 22.7 (*t*); 16.9 (*t*); 14.1 (*q*). EI-MS (70 eV): 376 (27, M^+), 262 (100), 156 (15), 142 (12), 105 (11), 91 (10), 44 (29). HR-ESI-MS: 376.3189 ($[M+H]^+$, $C_{24}H_{42}NO_2^+$; calc. 376.3215), 751.6324 ($[2M+H]^+$, $C_{48}H_{83}N_2O_4^+$; calc. 751.6352.

*(3a*R*,5*S*,8a*R*,9a*R*)-3a,5,6,7,8,8a,9,9a-Octahydro-5,8a-dimethyl-3-[(propylamino)methyl]-naphtho[2,3-*b*]furan-2(3*H*)-one* (**3h**). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.07 (*s*, 1 H); 4.67 (*s*, 1 H); 3.05 (*s*, 1 H); 2.82–2.92 (*m*, 2 H); 2.65–2.73 (*m*, 1 H); 2.50–2.59 (*m*, 2 H); 2.40 (*s*, 1 H); 2.02 (*d*, J = 14.4, 1 H); 1.69–1.85 (*m*, 2 H); 1.05 (*s*, 3 H); 1.03 (*d*, J = 7.2, 3 H); 0.83 (*t*, J = 7.6, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.0; 150.7; 115.1; 76.7; 51.9; 46.5; 45.6; 42.6; 42.1; 38.4; 37.7; 32.9; 32.8; 28.6; 23.0; 22.9; 16.8; 11.7. EI-MS (70 eV): 262 (100, M^+), 72 (38), 292 (25), 105 (24), 91 (23), 44 (21). HR-ESI-MS: 292.2275 ($[M+H]^+$, $C_{18}H_{30}NO_2^+$; calc. 292.2276), 583.4438 ($[2M+H]^+$, $C_{36}H_{59}N_2O_4^+$; calc. 583.4474), 605.4254 ($[2M+Na]^+$, $C_{36}H_{58}N_2NaO_4^+$; calc. 605.4294).

*(3a*R*,4a*S*,8a*R*,9a*R*)-Decahydro-8a-methyl-5-methylidene-3-[(propylamino)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**4h**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.69 (*s*, 1 H); 4.41 (br. *s*, 1 H); 4.38 (*s*, 1 H); 3.32 (*s*, 1 H); 2.93 (*dd*, J = 7.2, 11.6, 1 H); 2.83 (*dd*, J = 6.4, 13.6, 1 H); 2.67 (*dd*, J = 7.2, 11.2, 1 H); 2.48–2.56 (*m*, 2 H); 2.38–2.48 (*m*, 1 H); 2.07 (*d*, J = 15.2, 2 H); 1.85–1.94 (*m*, 1 H); 1.70 (*d*, J = 12, 1 H); 0.85 (*t*, J = 7.6, 3 H); 0.72 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.4; 149.3; 106.5; 78.4; 52.1; 47.4; 46.5; 45.3; 42.2; 41.4; 39.2; 36.8; 34.8; 23.0; 22.7; 21.2; 17.9; 11.8. EI-MS (70 eV): 292 (100, M^+), 262 (88), 44 (25), 293 (18), 72 (13), 58 (9). HR-ESI-MS: 292.2270 ($[M+H]^+$, $C_{18}H_{30}NO_2^+$; calc. 292.2276), 583.4436 ($[2M+H]^+$, $C_{36}H_{59}N_2O_4^+$; calc. 583.4474), 605.4253 ($[2M+Na]^+$, $C_{36}H_{58}N_2NaO_4^+$; calc. 605.4294).

*(3a*R*,4a*S*,8a*R*,9a*R*)-3-[(Hexylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]furan-2(3*H*)-one* (**4i**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.71 (*s*, 1 H); 4.41–4.45 (*m*, 1 H); 4.40 (*s*, 1 H); 2.96 (*dd*, J = 6.8, 11.6, 1 H); 2.85 (*dd*, J = 7.2, 13.6, 1 H); 2.70 (*dd*, J = 6.8, 11.6, 1 H); 2.52–2.62 (*m*, 1 H); 2.40–2.48 (*m*, 2 H); 2.22–2.30 (*m*, 1 H); 2.08 (*d*, J = 14.0, 1 H); 1.88–1.98 (*m*, 1 H); 1.73 (*d*, J = 12.4, 1 H); 0.82 (*t*, J = 7.2, 3 H); 0.74 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.4; 149.4; 106.6; 78.4; 50.4; 47.8; 46.6; 45.5; 42.3; 41.5; 39.2; 36.8; 34.9; 31.9; 30.0; 27.1; 22.8; 22.7; 21.2; 17.9; 14.1. EI-MS (70 eV): 262 (100,

M^+), 44 (33), 334 (16), 263 (15), 100 (14), 91 (10). HR-ESI-MS: 334.2744 ($[M+H]^+$, $C_{21}H_{36}NO_2^+$; calc. 334.2746), 667.5442 ($[2M+H]^+$, $C_{42}H_{71}N_2O_4^+$; calc. 667.5413).

*(3a*R*,5*S*,8a*R*,9a*R*)-3-[(Hexylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3i**). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.04 (br. *s*, 1 H); 4.67 (br. *s*, 1 H); 3.96 (*t*, *J* = 7.6, 1 H); 3.02–3.10 (*m*, 2 H); 2.95 (*dd*, *J* = 7.6, 15.2, 1 H); 2.83 (*t*, *J* = 7.6, 1 H); 2.70 (*dd*, *J* = 6.8, 11.6, 1 H); 2.52–2.59 (*m*, 1 H); 2.32–2.44 (*m*, 1 H); 1.99 (*dd*, *J* = 2.8, 14.4, 1 H); 1.95 (*s*, 1 H); 1.87 (*s*, 1 H); 1.14 (*s*, 3 H); 1.03 (*d*, *J* = 7.6, 3 H); 0.84 (*t*, *J* = 7.6, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.3; 151.1; 115.1; 77.6; 50.1; 45.5; 42.7; 42.2; 38.5; 37.8; 33.1; 32.8; 31.8; 29.7; 29.7*; 28.7; 26.9; 22.9; 22.6; 16.9; 14.1. EI-MS (70 eV): 262 (100, M^+), 44 (36), 334 (25), 114 (20), 263 (19), 105 (18). HR-ESI-MS: 334.2688 ($[M+H]^+$, $C_{21}H_{36}NO_2^+$; calc. 334.2746), 667.5447 ($[2M+H]^+$, $C_{42}H_{71}N_2O_4^+$; calc. 667.5413).

*(3a*R*,4a*S*,8a*R*,9a*R*)-3-[(Butylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]-furan-2(3*H*)-one* (**4j**). ^{1}H-NMR (600 MHz, $CDCl_3$): 4.69 (*s*, 1 H); 4.40 (br. *s*, 1 H); 4.38 (*s*, 1 H); 2.93 (*dd*, *J* = 6.8, 11.6, 1 H); 2.82 (*dd*, *J* = 7.2, 14.0, 1 H); 2.65 (*dd*, *J* = 7.2, 11.6, 1 H); 2.50–2.60 (*m*, 2 H); 2.38–2.44 (*m*, 1 H); 2.24 (br. *d*, *J* = 12.0, 1 H); 2.08 (*dd*, *J* = 1.6, 15.6, 1 H); 1.85–1.95 (*m*, 1 H); 1.70 (*d*, *J* = 12.0, 1 H); 0.83 (*t*, *J* = 7.6, 3 H); 0.72 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.3; 149.3; 106.5; 78.3; 49.9; 47.5; 46.5; 45.4; 42.2; 41.4; 39.1; 36.8; 34.8; 32.1; 22.7; 21.1; 20.5; 17.9; 14.1. EI-MS (70 eV): 306 (100, M^+), 262 (31), 307 (21), 44 (12), 263 (5). HR-ESI-MS: 306.2415 ($[M+H]^+$, $C_{19}H_{32}NO_2^+$; calc. 306.2433), 611.4831 ($[2M+H]^+$, $C_{38}H_{63}N_2O_4^+$; calc. 611.4787).

*(3a*R*,5*S*,8a*R*,9a*R*)-3-[(Butylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3j**). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.07 (br. *s*, 1 H); 4.67 (br. *s*, 1 H); 3.02–3.08 (*m*, 1 H); 2.81–2.86 (*m*, 2 H); 2.69 (*dd*, *J* = 7.2, 11.6, 1 H); 2.50–2.62 (*m*, 1 H); 2.34–2.44 (*m*, 1 H); 2.00 (*dd*, *J* = 2.8, 14.8, 1 H); 1.68–1.80 (*m*, 1 H); 1.15 (*s*, 3 H); 1.04 (*d*, *J* = 7.2, 3 H); 0.84 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.0; 150.7; 115.1; 77.4; 49.7; 46.5; 45.6; 42.6; 42.1; 38.4; 37.6; 32.9; 32.7; 31.9; 28.6; 22.8; 20.3; 16.7; 13.9. EI-MS (70 eV): 262 (100, M^+), 306 (47), 44 (35), 105 (19), 86 (16). HR-ESI-MS: 306.2442 ($[M+H]^+$, $C_{19}H_{32}NO_2^+$; calc. 306.2433).

*(3a*R*,4a*S*,8a*R*,9a*R*)-3-[(Decylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-*b*]-furan-2(3*H*)-one* (**4k**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.68 (*s*, 1 H); 4.41 (br. *s*, 1 H); 4.37 (*s*, 1 H); 2.93 (*dd*, *J* = 7.2, 11.6, 1 H); 2.83 (*dd*, *J* = 6.4, 13.2, 1 H); 2.67 (*dd*, *J* = 6.8, 11.6, 1 H); 2.50–2.60 (*m*, 2 H); 2.24 (br. *d*, *J* = 12.4, 2 H); 2.06 (br. *d*, *J* = 16.4, 1 H); 1.85–1.95 (*m*, 1 H); 1.70 (*d*, *J* = 12.0, 1 H); 0.78 (*t*, *J* = 6.8, 3 H); 0.71 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.4; 149.3; 106.5; 78.3; 50.2; 47.4; 46.5; 45.4; 42.2; 41.4; 39.1; 36.8; 34.8; 31.9; 29.9; 29.6 (br., 4 C); 29.5; 29.4; 27.3; 22.7; 21.2; 17.8; 14.2. EI-MS (70 eV): 262 (100, M^+), 390 (80), 44 (27), 391 (21), 263 (18). HR-ESI-MS: 390.3333 ($[M+H]^+$, $C_{25}H_{44}NO_2^+$; calc. 390.3372).

*(3a*R*,5*S*,8a*R*,9a*R*)-3-[(Decylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one* (**3k**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.99 (br. *s*, 1 H); 4.54–4.58 (*m*, 1 H); 2.92–2.98 (*m*, 1 H); 2.72–2.82 (*m*, 1 H); 2.57 (*dd*, *J* = 6.8, 10.8, 1 H); 2.40–2.50 (*m*, 2 H); 2.25–2.35 (*m*, 1 H); 1.91 (*dd*, *J* = 2.4, 14.8, 1 H); 1.60–1.68 (*m*, 1 H); 1.05 (*s*, 3 H); 0.95 (*d*, *J* = 7.2, 3 H); 0.70 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.9; 150.6; 115.4; 77.7; 50.1; 46.7; 45.7; 42.8; 42.2; 38.5; 37.7; 32.9; 32.8; 31.9; 30.0; 29.6 (br., 4 C); 29.4; 28.7; 27.4; 22.9; 22.7; 16.9; 14.1. EI-MS (70 eV): 262 (100, M^+), 390 (66), 44 (30), 158 (24), 391 (17). HR-ESI-MS: 390.3351 ($[M+H]^+$, $C_{25}H_{44}NO_2^+$; calc. 390.3345).

*(3a*R*,4a*S*,8a*R*,9a*R*)-Decahydro-8a-methyl-5-methylidene-3-[(undecylamino)methyl]naphtho[2,3-*b*]furan-2(3*H*)-one* (**4l**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.71 (*s*, 1 H); 4.44 (br. *s*, 1 H); 4.40 (*s*, 1 H); 2.89–3.00 (*m*, 2 H); 2.70–2.80 (*m*, 1 H); 2.55–2.63 (*m*, 1 H); 2.42–2.50 (*m*, 1 H); 2.26 (*d*, *J* = 12.8, 1 H); 2.10 (*d*, *J* = 15.6, 1 H); 1.90–1.99 (*m*, 1 H); 1.72 (*d*, *J* = 12.0, 1 H); 0.82 (*t*, *J* = 7.2, 3 H); 0.74 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.5; 149.4; 106.7; 78.5; 50.3; 47.4; 46.7; 45.5; 42.4; 41.6; 39.3; 36.9; 34.9; 32.1; 29.9 (br., 6 C); 29.5; 27.5; 22.9; 21.3; 18.0; 14.4. EI-MS (70 eV): 262 (100, M^+), 44 (37), 41 (22), 170 (19), 172 (17). HR-ESI-MS: 404.3529 ($[M+H]^+$, $C_{26}H_{46}NO_2^+$; calc. 404.3528).

*(3a*R*,5*S*,8a*R*,9a*R*)-3a,5,6,7,8,8a,9,9a-Octahydro-5,8a-dimethyl-3-[(undecylamino)methyl]naphtho-[2,3-*b*]furan-2(3*H*)-one* (**3l**). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.09 (*s*, 1 H); 4.68 (br. *s*, 1 H); 3.10–3.02 (*m*, 1 H); 2.86–2.98 (*m*, 2 H); 2.70 (*dd*, *J* = 6.4, 10.8, 1 H); 2.50–2.57 (*m*, 2 H); 2.38–2.48 (*m*, 1 H); 2.03 (*d*, *J* = 15.2, 1 H); 1.17 (*s*, 3 H); 1.06 (*d*, *J* = 8.0, 3 H); 0.81 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.3; 151.2; 115.2; 77.5; 50.3; 46.7; 45.8; 42.9; 42.4; 38.7; 37.9; 33.2; 33.1; 32.1; 29.9; 29.8 (br., 4 C); 29.6; 28.9; 27.5; 23.1; 22.9; 17.1; 14.4. EI-MS (70 eV): 262 (100, M^+), 207 (81), 171 (72), 217 (67), 91 (54). HR-ESI-MS: 404.3542 ($[M+H]^+$, $C_{26}H_{46}NO_2^+$; calc. 404.3528).

(3aR,4aS,8aR,9aR)-3-[(Dodecylamino)methyl]decahydro-8a-methyl-5-methylidenenaphtho[2,3-b]furan-2(3H)-one (**4m**). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.70 (*s*, 1 H); 4.41 (br. *s*, 1 H); 4.39 (*s*, 1 H); 2.90–2.96 (*m*, 1 H); 2.82–2.89 (*m*, 1 H); 2.65–2.72 (*m*, 1 H); 2.53–2.62 (*m*, 2 H); 2.41–2.45 (*m*, 1 H); 2.25 (*d*, $J = 12.4$, 1 H); 1.70 (*d*, $J = 12.0$, 1 H); 0.79 (*t*, $J = 6.8$, 3 H); 0.73 (*s*, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.4; 149.3; 106.5; 78.3; 50.3; 47.4; 46.5; 45.4; 42.3; 41.5; 39.2; 36.8; 34.8; 31.9; 29.9; 29.7; 29.6 (br., 5 C); 29.4; 27.4; 22.8; 21.2; 17.9; 14.2. EI-MS (70 eV): 262 (100, M^+), 207 (62), 44 (43), 91 (63), 281 (32). HR-ESI-MS: 418.3720 ($[M+H]^+$, $C_{27}H_{48}NO_2^+$; calc. 418.3685).

(3aR,5S,8aR,9aR)-3-[(Dodecylamino)methyl]-3a,5,6,7,8,8a,9,9a-octahydro-5,8a-dimethylnaphtho[2,3-b]furan-2(3H)-one (**3m**). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.06 (br. *s*, 1 H); 4.67 (br. *s*, 1 H); 3.01–3.10 (*m*, 1 H); 2.88–2.90 (*m*, 2 H); 2.69 (*dd*, $J = 7.2$, 12.0, 1 H); 2.56–2.59 (*m*, 2 H); 2.36–2.42 (*m*, 1 H); 2.22–2.30 (*m*, 2 H); 2.02 (*dd*, $J = 2.8$, 14.8, 1 H); 1.16 (*s*, 3 H); 1.05 (*d*, $J = 7.6$, 3 H); 0.79 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 178.3; 150.9; 115.2; 77.5; 50.2; 46.7; 45.7; 42.8; 42.3; 38.6; 37.8; 33.1; 32.9; 31.9; 29.9; 29.7 (br., 5 C); 29.4; 28.7; 27.4; 23.0; 22.8; 16.9; 14.2. EI-MS (70 eV): 262 (100, M^+), 207 (95), 281 (49), 209 (43), 217 (40). HR-ESI-MS: 418.3734 ($[M+H]^+$, $C_{27}H_{48}NO_2^+$; calc. 418.3685).

Aedes aegypti. The Orlando strain of *Ae. aegypti* was reared in the insectary of the Mosquito and Fly Research Unit at Center for Medical, Agricultural, and Veterinary Entomology (CMAVE), USDA-ARS. The Orlando strain of *Ae. aegypti* has been established in CMAVE since 1952. Female adults were used for all experiments, since only females take blood meals and are the main concern of the general public. Eggs were hatched by placing a square of a paper towel with eggs in a flask filled with 1000 ml of dist. H_2O containing 40 mg of larval diet (3 : 2 brewer's yeast/liver powder (*MP Biomedicals*, Irvine, CA)). The hatched larvae were held overnight in the flask, and 200 larvae were transferred to a 4-l plastic tray containing 2 l of dist. H_2O. Larval diet was added to each tray according to the following schedule: day 1, 80 mg; day 3, 40 mg; day 4, 80 mg; day 5, 120 mg; and day 6, 150 mg. Mosquitoes were reared in an environmental chamber set with a temp. profile representing a simulated summer day regime (ranging from 22 to 30°) and 80% relative humidity (RH). Incandescent lighting was set to a crepuscular profile with a photoperiod of 14 : 10 light/dark (L/D) h, including 2 h of simulated dawn and 2 h of simulated dusk. Adults were held in a screened cage and provided 10% sucrose *ad libitum*. Bovine blood in 1% heparin that had been placed in a pig intestine and warmed to 37° was provided to adults twice a week. Eggs were collected on paper towels (*Vasco Brands*, Elmira, NY) that lined the rim of H_2O containers. These egg-laden papers were air-dried at 27° and 80% RH for 24 h, and stored in containers with 100% humidity for 3–30 d. When needed, eggs were hatched under vacuum and larvae were reared in containers as described above.

Larvae Bioassays. Larval bioassays were performed as described in [30]. Briefly, five first instar larvae of *Ae. aegypti* were added to each well of 24-well plates. Deionized H_2O (950 µl) and larval diet (40 µl) were then added to each well. All chemicals to be evaluated were diluted in acetone. Decreased concentrations were used to further group the chemicals as highly active, moderately active, slightly active, or highly inactive. Dil. chemicals (10 µl) were then added to each well containing a total volume of 1 ml of larvae, food, and H_2O. As control treatments, 10 µl of acetone alone was added to each well. Larval mortality was recorded after 24 h of exposure. The larval assays were repeated several times on different days with six concentrations providing a range of 0–100% mortality.

Adult Bioassays. To determine the toxicity of each chemical against female *Ae. aegypti*, chemicals were serially diluted in acetone and topically applied to individual mosquitoes. Prior to topical application, 5–7-day-old females were briefly anaesthetized for 30 s with CO_2 and placed on a 4° chill table (*BioQuip Products*, Rancho Dominguez, CA). A droplet of 0.5 µl of chemical soln. was applied to the dorsal thorax using a *700* series syringe and a *PB 600* repeating dispenser (*Hamilton*, Reno, NV). Six concentrations providing a range of 0–100% mortality were used on 25–30 females per concentration. Tests were replicated three times. Control treatments with 0.5 µl of acetone alone gave control mortality with less than 10%. After treatment, mosquitoes were kept in plastic cups and supplied with 10% sucrose soln. for 24 h before mortality was recorded. Temp. and humidity were maintained at 26° and 80% RH, resp. Every bioassay was conducted at 27° and 80% RH and replicated three times. Bioassay data were analyzed using PoloPlus probit and logit analysis software (*LeOra Software*, Petaluma, CA). Chi-squared goodness of fit test was performed, and LD_{50}/LD_{95} values were calculated using PoloPlus program.

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